

Inflammatory arthritis

Do statins offer therapeutic potential in inflammatory arthritis?

I B McInnes, D W McCarey, N Sattar

Statins may reduce inflammation and modify vascular risk

Rheumatoid arthritis (RA) is associated with accelerated vascular risk with attendant early mortality (pooled standardised mortality rate 1.7) and excess morbidity.¹ Optimal treatment of RA disease activity should therefore reasonably deal with vascular risk modification in addition to the well recognised objectives of treatment—namely, to suppress inflammation, improve function, prevent articular damage, and modify psychosocial implications of disease. Intriguingly, vascular specialists are now exercised with the realisation that inflammation is central to the pathogenesis of atherogenesis. Striking similarities in the atherogenic lesion in the vessel have been drawn with the chronic synovitis characteristic of RA, particularly to plaque structure and the role of extracellular matrix degradation in subsequent rupture. That said, vascular inflammation is not reflected in the same degree of local tissue destruction, nor the sustained substantial increase in the acute phase response as in RA, but rather with a lower grade chronic inflammatory response relying on high sensitivity assays for detection of the persistent inflammatory load. Thus, although not necessarily exemplary of shared aetiology, these parallels suggest that shared interventions may be possible.

HMG-CoA reductase inhibitors (statins) reduce cardiovascular morbidity and mortality by around 25–50% and are widely used in primary and secondary prevention of vascular disease syndromes.^{2–4} Although operating in part through lipid modulation, recent studies demonstrate broader properties for statins, particularly in altering inflammatory pathways.⁵ There is considerable current interest, therefore, in the broader clinical uses of statins, in particular in disease states more clearly associated with high grade inflammation.

Many in vitro and animal studies now describe the potential anti-inflammatory effects of statins. After exposure to statins, endothelial cells exhibit increased endothelial nitric oxide synthase and tissue plasminogen activator antigen with reduced plasminogen

activator inhibitor 1, tissue factor, and endothelin expression (reviewed by Palinski and Napoli⁶). Macrophage chemokine release, chemotactic responses, and oxidative burst are reduced by statins, as is NK cell cytotoxicity in vitro. Antineutrophil cytoplasmic antibody-induced neutrophil activation is also suppressed in vitro.⁷ Together these effects suggest that innate immune responses may be susceptible to inhibition of HMG-CoA reductase.

“Will the anti-inflammatory effects of statins in animals be found in man?”

Similarly, effects on acquired immune responses have emerged. Statins suppress antigen presenting cell major histocompatibility complex II expression through CIITA modulation,⁸ T cell-macrophage interactions through leucocyte function antigen-1/intercellular adhesion molecule-1 (LFA-1/ICAM-1)⁹ T cell proliferation and interferon γ release, and modify polarisation of Th1 responses in vitro and in vivo in rodent models.^{10–11} In vivo suppressive effects by various statin moieties have been described in rodent experimental allergic encephalomyelitis,¹² carageenan induced inflammation,¹³ renal ischaemia reperfusion injury,¹⁴ and transplant models.¹⁵ There is, however, a marked absence of trial data in man to confirm these observations in vivo.

Synovial inflammation in RA is similarly characterised by activated components of both innate and acquired immune responses. RA synovitis contains a predominant Th1 response, widespread macrophage, fibroblast, mast cell, and B cell activation that in turn generate high autoantibody production (for example, anti-CCP, rheumatoid factors) and cytokine release (for example, tumour necrosis factor α (TNF α), interleukin (IL)1 β , IL6, IL15, and IL18). Endothelial cell activation, up regulated adhesion molecule expression, and angiogenesis are increasingly recognised. Thus numerous postulated effects for statins might operate within the synovial membrane. We have

recently shown in vitro suppression of synovial T cell and fibroblast-like synovocyte cytokine release by simvastatin, lending support to this notion. Moreover, we extended these studies to show that simvastatin effectively reduced the severity of rodent collagen induced arthritis in vivo.¹⁰ Ex vivo analysis in the latter studies showed suppression of Th1 responses to recall antigen responses (type II collagen) without generation of a compensatory Th2 response. This is in contrast with studies in experimental allergic encephalomyelitis, in which atorvastatin induced suppression of Th1 mediated neurological damage associated with enhancement of an antigen specific Th2 response.¹² Taken together there is some evidence on which to build hypotheses whereby statins might be useful in the treatment of RA.

Upon what basis might statins be used in RA? We believe that there are at least three areas which should be explored for the use of statins, including (a) examining vascular risk; (b) as immune modulators; or more likely (c) as “add on” treatment to existing treatments. Moreover, it is likely that elucidation of downstream molecular pathways targeted by statins might be more useful than HMG-CoA reductase inhibitors themselves in immune modulation. The existing statins have been developed for their ability to reduce cholesterol rather than as dual immune and lipid modulatory agents. Newer agents in development may be required to properly capture this therapeutic opportunity. One metabolite downstream from HMG-CoA reductase—namely, geranylgeranyl pyrophosphate (GGPP), excites particular interest. Numerous investigators have demonstrated that addition of GGPP to various models in which statins mediate anti-inflammatory, antithrombotic, or vasculoprotective effects will abrogate such actions.^{16–18} This suggests that statins may inhibit prenylation of signalling molecules such as the Rho family GTPases to suppress inflammation, and that specific prenylation inhibitors may be useful in autoimmune mediated inflammation.

POTENTIAL BENEFITS OF VASCULAR RISK IN RA

Accelerated atherogenesis is a major cause of morbidity and mortality in RA. Although RA is not typically associated with a raised cholesterol concentration, the characteristic dyslipidaemia is atherogenic with the common finding of low high density lipoprotein cholesterol and small dense atherogenic low density lipoprotein particles. Interestingly, lipid lowering even within the

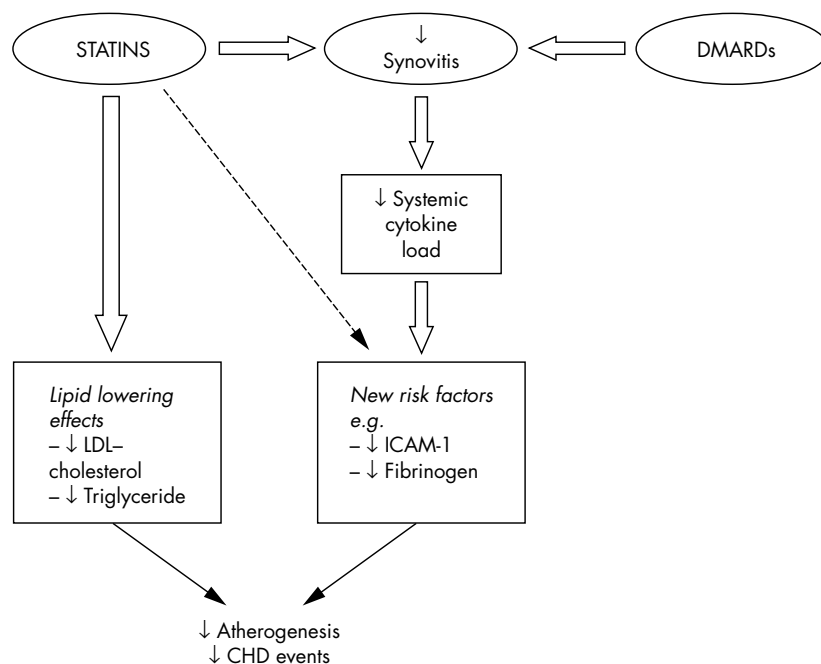


Figure 1 Potential mechanisms by which statins could reduce the risk of CHD in patients with RA. Statins may have a dual benefit in patients with RA. Firstly, their lipid lowering effects should directly reduce the CHD risk. Secondly, their anti-inflammatory effects, manifest within the synovial joint and thus acting to reduce systemic cytokine spill, will lead to downstream improvements in new risk factors, as indicated. Of course, statins may also convey direct anti-inflammatory effects at the vasculature. DMARD treatment clearly has a greater effect than statins in reducing synovial inflammation and there is emerging evidence that such treatments also improve new risk factor status (reviewed by Sattar *et al*¹⁹), and consequently reduce CHD risk.

“normal” cholesterol range has been shown to have vascular benefit,² and thus a direct coronary heart disease (CHD) protective pathway in RA for statins by traditional risk factor modification is likely.

We recently proposed that cytokine mediated inflammatory pathways can, in part, explain increased vascular risk through accentuation of both classical (lipids) and new (endothelial function, insulin resistance) pathways.¹⁹ Possibly, anti-inflammatory mechanisms with accompanying downstream improvements in new risk factor pathways may operate for statins. Firstly, statins could reduce C reactive protein (CRP), an established independent risk factor for CHD²⁰; possibly, CRP itself is directly atherogenic through a range of mechanisms.^{21–24} Secondly, we have shown that statins suppress IL6 release *in vitro*.¹⁰ A chronic increase of IL6 may promote atherogenesis directly through effects in the vessel wall and indirectly through secondary effects on, for example, insulin resistance.²⁵

“Statins not only control RA disease activity but also reduce vascular risk”

In theory statins could also modify plasma viscosity, fibrinogen, and ICAM-1, markers of hypercoagulability and

endothelial activation, respectively, in patients with active RA. The idea that the inflammation modulation may alter vascular risk in RA is emerging. A recently reported prospective study of patients with RA suggests that treatment with methotrexate may increase the length of survival, this being largely attributable to a reduction in cardiovascular mortality.²⁶ Moreover, it has been known for some time that corticosteroid treatment has the surprising effect of partially reversing insulin resistance in patients with previously untreated, active RA.²⁷ Similarly, patients in whom sulfasalazine has suppressed the inflammatory response demonstrate normalisation of glucose handling.²⁷ More recently, TNF α blockade with infliximab has been shown to improve endothelial function in patients with RA.²⁸ It may therefore be argued that suppression of inflammation not only controls RA disease activity but also modifies various recently elucidated pathways whereby vascular risk is increased in active RA.

STATINS AS IMMUNE MODULATORS IN INFLAMMATORY DISEASE IN MAN

Statins may reduce rejection after solid organ transplantation by immunomodulatory effects; however, published

studies are contradictory and do not permit firm conclusions. A pilot study of pravastatin in kidney transplant recipients showed significantly reduced acute rejection rates,²⁹ and the same drug reduced severe rejection with haemodynamic compromise in patients after cardiac transplantation.³⁰ However, an international, multicentre, randomised, placebo controlled trial of fluvastatin after renal transplantation did not reduce allograft rejection.³¹ Furthermore, simvastatin was shown to increase long term survival and reduce rates of graft vessel disease in patients with cardiac transplants, but had no significant effect on rejection rates in a 4 year follow up study.³²

It has been suggested that statins may be beneficial in multiple sclerosis. A small, open label, uncontrolled trial of simvastatin 80 mg daily was recently reported, demonstrating a reduced number of gadolinium enhancing magnetic resonance imaging lesions in patients with relapsing-remitting disease.³³ It had no effect on the clinical relapse rate and clearly larger, more rigorous studies will be required to define the role for statin treatment in this disease.

We recently performed the first placebo controlled study to examine therapeutic effects and vascular risk factor modification by statins in a chronic autoimmune disease.³⁴ In a randomised, double blind, placebo controlled trial, we found that atorvastatin (40 mg/day) suppressed the disease activity score (~10%), acute phase parameters (CRP (50%) and erythrocyte sedimentation rate (28%)), and significantly reduced the swollen joint count (2.16 joints relative to placebo change) in patients with RA presenting with active disease despite existing disease modifying anti-rheumatic drug (DMARD) treatment. Although the magnitude of change with atorvastatin was modest, a significant reduction in the disease activity score, nevertheless, provides the first clinical indication that pathways targeted by statins may be useful in the treatment of inflammatory disease. However, no effect was observed on other clinical measures of disease activity, particularly the Health Assessment Questionnaire, and larger studies will be required to determine the extent to which changes seen in this study will be useful clinically.

In parallel, and as suggested above, our data clearly demonstrate that statins are potentially effective in modifying classical (lipids) and new risk factors of vascular disease despite the presence of “high grade” inflammation. Indeed, we noted that atorvastatin reduced plasma viscosity, fibrinogen, and IL6

concentrations relative to placebo. Thus potential biphasic benefit in reduced inflammation and modified vascular risk may accrue with the use of statins in RA (fig 1).

Whether distinct effects for different statins will emerge that are functionally important is unclear. Distinct function could arise from discrete pharmacological properties—for example, lipid solubility, or from subtleties of chemical structure—for example, the LFA binding capacity of lovastatin. More detailed and extensive analyses of a range of in vitro and in vivo models are required to examine such fundamental comparative issues. Crucial to this will be the development of new therapeutic moieties based on targeting downstream pathway studies as discussed above.

Most patients with RA now receive a combination of DMARDs as the emphasis of treatment moves towards the induction of disease amelioration/remission together with tissue protection. Whereas existing DMARD treatment may partially reverse vascular risk,²⁶ our recent report³⁴ suggests that atorvastatin may operate to reduce both traditional and new vascular risk factors. Clearly, longitudinal studies are now required to determine whether such benefits of statins translate into a significant reduction of the vascular risk end point in patients with RA, and if so, whether this occurs with minimal toxicity. Given the dual effects of statins in RA, it is even possible that the relative magnitude of benefit from such treatments may be greater in RA than in non-inflamed controls. Finally, statin sensitive biochemical pathways offer further opportunity for the generation of new disease modifying drugs to treat chronic inflammatory diseases.

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Authors' affiliations

I B McInnes, D W McCarey, N Sattar, Centre for Rheumatic Diseases and Department of Vascular Biochemistry, University of Glasgow, Glasgow Royal Infirmary, Glasgow G31 2ER, UK

Correspondence to: Professor I B McInnes, ibmi1w@clinmed.gla.ac.uk

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